ROLE OF FATTY ACIDS IN THE CONTROL OF LEUKOCYTE FUNCTION AND IN THE ESTABLISHMENT OF DIABETES

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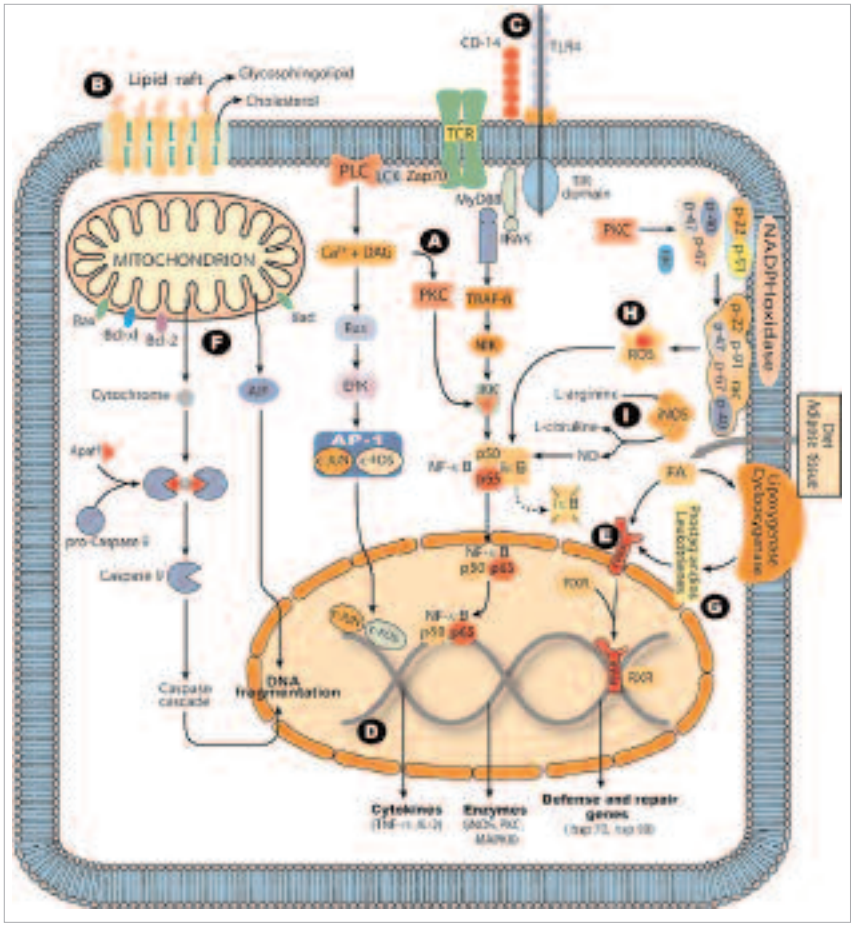
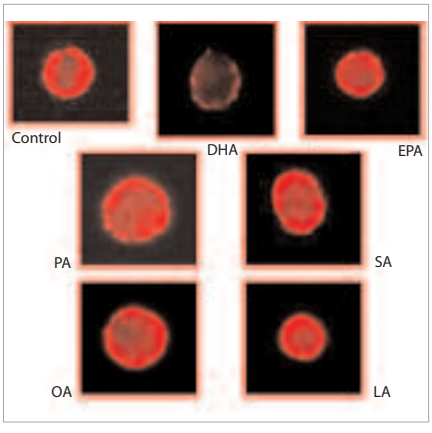
Previous studies of our group have determined that fatty acids (FA) can function as signaling factors in intercellular interactions, regulating several aspects of leukocyte function (mainly lymphocytes and macrophages) and insulin secretion by beta cells of pancreatic islets. In this project we focus the investigation on the mechanisms of action of fatty acids. The first site of interaction of fatty acids in the cell is the plasma membrane which leads us to investigate the interactions between FA and the lipid bilayer in model membranes and isolated cells. The effects of FA in the intracellular signaling pathways will be investigated as well as the involvement of receptors (like the PPAR) and transcription factors (NFÎB and AP1). In Langerhans islets the effects of FA on the insulin signaling pathways and on the activation of the enzymatic complex NADPH oxidase (that was identified by us in rat Langerhans islets) will be investigated. The toxicity of FA has been clearly evidenced by our group in lymphocytes and macrophages and will be now studied in neutrophils, by using *in vivo* and *in vitro* models. The persistence (or exacerbation) of the effects of FA administration, particularly fish oil, will be assessed by its administration during two generations of rats. These issues complete our investigation on the mechanisms of FA action. It is necessary to determine whether the toxicity of FA occurs indistinctly for all leukocytes and whether the use of fish oil (as alimentary supplement) can modify the immune function and ensure a better life quality to our descendents.



SUMMARY OF THE POSSIBLE MECHANISMS BY WHICH FATTY ACIDS MODULATE LEUCOCYTE FUNCTION
(A) Activation of intracellular signalling pathways; (B) activation of lipid-raft-associated proteins; (C) binding to Toll Like Receptors; (D) regulation of gene expression; (E) activation of transcription factors; (F) induction of cell death; (G) production of eicosanoids; (H) production of reactive oxygen species; and (I) production of reactive nitrogen species. Apaf-1, apoptotic protease-activating factor-1; AIF, apoptosis-inducing factor; Bax, Bcl-2 associated X protein; Bad, Bcl-2-associated death promoter; Bcl-xl, B-cell lymphoma X (long form); IKK, IÎB kinase; IRAK, IL-1 receptor-associated kinase; LK, leucocyte-specific protein tyrosine kinase; MyD88, myeloid differential factor 88; NIK, NFÎB-inducing kinase; TRAF-6, TNFR-associated factor 6; TIR, Toll/IL-I receptor/resistance domain; Zap70, zeta-chain-associated protein kinase 70

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Macrophage and lymphocyte convert glucose and glutamine into lipids (fatty acids, phospholipids and cholesterol). These lipid molecules are accumulated inside the cells, released to the medium or transferred to leukocytes and other cell types such as insulin-secreting cells. This phenomenon regulates several functions of the acceptor cells, such as lymphocyte proliferation and macrophage phagocytosis. This is a new intercellular communication mechanism that may play an important role in certain tissue microenvironments.



Effect of docosahexaenoic (DHA), eicosapentaenoic (EPA), stearic (SA), palmitic (PA), oleic (OA) and linoleic (LA) acids on the distribuition of lipid rafts in the membrane. Lymphocytes were marked with CT-B conjugated to 594-Alexa. Fluorescence was then monitored by fluorescence microscopy under 100x magnification. Cells were evaluated by fluorescence microscopy. All images are from a representative experiment involving three different assays with similar results

Dietary lipids regulate various leukocyte functions such as lymphocyte proliferation, macrophage and neutrophil phagocytosis, and production of nitric oxide, reactive oxygen species and cytokines. The fatty acids also control gene expression and phosphorylation of proteins as those of the interleukin-2 signaling pathway in lymphocytes.

High plasma levels of fatty acids (as observed in prolonged exercise, fasting and diabetes) are associated with the occurrence of leukocyte death. In critically ill patients, the lipid content of parenteral diet also causes leukocyte death. In turn, linoleic and oleic acids accelerate the wound healing process and ω-3 fatty acids present beneficial effects on tumor growth and cachexia.

Saturated fatty acids decrease the activity of the insulin signaling pathway, cause oxidative stress, raise nitric oxide production, and impair mitochondrial function in skeletal muscle. On the other hand, high levels of fatty acids lead insulin-secreting cells to death. This effect involves changes in protein phosphorylation and production of reactive oxygen species. The presence of NADPH oxidase activity in pancreatic beta cells was shown for the first time as well as its regulation by glucose, fatty acids and cytokines. These effects of the fatty acids might be involved in the establishment of diabetes (types I and II).

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